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Filed: January 28, 2000

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by deprotection steps and washing steps. See generally Gait, Oligonucleotide Synthesis: A Practical Approach, IRL Press, Oxford, UK 1984; incorporated by reference. This is generally done either with phosphoramidite or H-phosphonate nucleosides. This is generally done in one of two ways. First, the 5' position of the ribose is protected with 4',4-dimethoxytrityl (DMT) followed by reaction with either 2-cyanoethoxy-bis-diisopropylaminophosphine in the presence of diisopropylammonium tetrazolide, or by reaction with chlorodiisopropylamino 2'-cyanoethoxyphosphine, to give the phosphoramidite as is known in the art; although other techniques may be used as will be appreciated by those in the art. See Gait, supra; Caruthers, Science 230:281 (1985), both of which are expressly incorporated herein by reference.

In the Drawings:

Please amend the drawings as amended in the drawings submitted herewith.

REMARKS

Claims 27-32 are pending. Claims 1-26 are canceled as drawn to non-elected inventions. Claims 27-32 stand rejected under 35 U.S.C. §112, second paragraph as being indefinite; under 35 U.S.C. §102(b) as being anticipated by GB 1 241 539 ("American Hospital Supply"); and under 35 U.S.C. §103(a) as being obvious over American Hospital Supply in view of FR 2.156.519 ("IMMUNO AG").

Response to Detailed Action

Priority

Applicants have amended the claim of priority and acknowledge that January 29, 1999 is the correct filing date of the Provisional Application.

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Oath/Declaration

The defective declaration, as noted by the Examiner, has been revised. Attached hereto is the revised Declaration.

Drawings

The drawings have been amended to incorporate to comments of the Examiner. No new matter was added to the Specification to make these changes. Support for these changes can be found on Page 3 line 35 and Page 4 lines 1 through 17 of the above-referenced Application.

Rejection Under 35 U.S.C. §112, second paragraph

Claims 27-32 stand rejected under U.S.C. §112, second paragraph as being indefinite. More particularly, Examiner states Claims 27 and 28 are indefinite because it is not clear how the recited waste reservoir structurally cooperates with the claimed rotor.

Claim 27 has been amended to recite with more particularity that which the Applicants consider as the invention. In particular, the centrifuge is now claimed, and not merely part of the preamble of Claim 27. Applicants refer the Examiner to page 14 in the Detailed Description of the Invention, lines 14-25. The specification clearly sets forth the how the waste reservoir structurally cooperates with the claimed rotor. The amendment and citation vitiate the Examiner's §112 rejection of Claims 27 and 28.

Next, Applicants refer the Examiner to pages 5 and 15, lines 29-35 and 21-35, respectively. The specification clearly sets forth structural cooperation between the structures of a liquid distribution system and computer. The specification states, *inter alia*, "the

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centrifuge is configured to have a tube or pipe leading to a waste reservoir ... gravity flow of the expelled liquids can then lead to collection of the waste outside the centrifuge.” Page 14, lines 23-25. The aforementioned references vitiate the Examiner’s §112 second paragraph rejection of Claims 30-32. As such Applicants respectfully request the Examiner to withdraw the rejections.

Rejection Under 35 U.S.C. §102(b)

The Examiner rejects Claims 27, 28, and 30-32 under 35 U.S.C. §102(b) as being anticipated by American Hospital Supply (GB 1 241 539). More particularly, Examiner argues that the reference of American Hospital Supply discloses a centrifuge device which includes a rotor, which holds reaction vessels in a tilted position. Examiner further states that the reaction vessels are communicated with a waste reservoir with a tube; and the rotor includes a liquid distribution system and the centrifuge is controlled by a computer. Applicants respectfully traverse.

American Hospital Supply recites a centrifuge apparatus for washing and treating blood cells. *American Hospital Supply*, GB 1 241 539, page 1, line 77-78. The invention calls for washing fluids to be forcefully introduced into each tube at the open end thereof as such tube is traveling rapidly about an axis of centrifugation. *American Hospital Supply*, GB 1 241 539, page 1, line 55-59. The reaction tubes of this disclosed invention tilt inward, toward the axis of rotation. *American Hospital Supply*, GB 1 241 539, Figures 3, and 6-8.

In contrast the present invention provides a centrifuge with a rotor to hold reaction vessels at a tilt away from the axis of rotation. (*see* Claim 27). The apparatus also provides for a waste reservoir, which is connected to the centrifuge, designed to hold the liquids that are expelled from the reaction vessels. *Id.*

An anticipation rejection requires that a single reference expressly or inherently disclose each and every element of a claim. *In re Paulsen*, 31 USPQ2d 1671, 1672 (Fed. Cir.

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1994); MPEP §2131 (citing *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)). Additionally, the reference must enable and describe the claimed invention “sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention.” *Id.* at 1673. To be enabling, the reference must teach the skilled artisan to make and use the full scope of the claimed invention without undo experimentation. *See Genentech Inc. v. Novo Nordisk A.S.*, 42 USPQ2d 1001, 1004 (Fed Cir. 1997).

Although the Examiner is correct in noting that the reference of American Hospital Supply discloses a centrifuge device, which includes a rotor, which holds reaction vessels in a tilted position, and the vessels are communicated with a waste reservoir that is controlled by a computer, nothing in American Hospital Supply teaches or suggests a centrifuge with a rotor to hold reaction vessels at a tilt away from the axis of rotation. Rather, and in distinct contrast to the claimed invention, American Hospital Supply teaches that the reaction tubes tilt inward, toward the axis of rotation.

Therefore, American Hospital Supply does not anticipate Claims 27, 28, and 30-32. Accordingly, Applicants respectfully submit that Claims 27, 28, and 30-32 are patentably distinct from American Hospital Supply. Applicants respectfully request the withdrawal of the rejection of Claims 27, 28, and 30-32 under 35 U.S.C. §102(b) as being anticipated by American Hospital Supply.

Rejection Under 35 U.S.C. §103(a)

The Examiner rejects Claim 29 under 35 U.S.C. 103(a) as being unpatentable over American Hospital Supply in view of IMMUNO AG.

The American Hospital Supply reference has been adequately discussed above.

IMMUNO AG. was written in French, but no translation was obtained. Referring to Figure 2, Applicants note that IMMUNO AG. discloses a rotor structure for a centrifuge device which can support a tube or microplate in a tilted manner. Applicants also note the direction of

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the tilt of the tube in the centrifuge. The opening of the tube points towards the axis of rotation, not away from it.

The present invention has been adequately discussed above.

The Examiner's basic position is that it would have been obvious for one of ordinary skill in the art to combine the microplate of IMMUNO AG with the rotor of American Hospital Supply. Applicants respectfully traverse the rejection. Applicants submit that the prior art references, taken alone or in combination, do not teach or suggests the present invention.

When rejecting claims under 35 U.S.C. §103(a), the Examiner must establish a *prima facie* case of obviousness. *See, e.g. In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993); MPEP §2142. A *prima facie* case requires 1) that the prior art must provide one of ordinary skill with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention; 2) the prior art must provide one of ordinary skill with a reasonable expectation of success; and 3) the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP §706.02(j).

To this end Applicants submit that the Examiner has fail to point to any motivation for the combination of the references. While the Examiner suggests that it would have been obvious to combine the references, they have pointed to no teaching in the prior art that would have motivated the skilled artisan to do so. The Examiner suggests that the skilled artisan would have made the combination for the "known and expected" result of providing an alternative means recognized in the art to achieve the same results and that the use of a microplate facilitates the handling and processing of multiple samples. However, Applicants note that nowhere in the prior art is the need for handling and processing more samples than would be held in a standard centrifuge rotor suggested. Accordingly, Applicants submit that there is no motivation to combine the references.

Assuming *arguendo*, that there was a motivation to combine the references, if the proposed modification renders the prior art unsatisfactory for its intended purpose, then there is

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no suggestion or motivation. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984), *see also* MPEP §2143.02. Furthermore, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959) *see also* MPEP §2143.02.

In this case, the cited prior art centrifuges are designed to retain samples in the tubes or plates, not to expel liquid from them.

The Examiner asserts that the claimed invention differs from American Hospital Supply by reciting the use of a microtiter plate as a reaction vessel, but IMMUNO AG. discloses a rotor structure for a centrifuge device which can support a tube or microplate in a tilted manner. Here, there is no motivation to combine, because if the tubes or microtiter plates were tilted away from the axis of rotation (as in the present invention) the tilt would render the prior art unsatisfactory for its intended purpose and change the principle of operation of the prior art invention. With respect to IMMUNO AG. Figure 2 again, the tilt of the microplate is not the same as the tilt of the claimed invention. There is no suggestion in either of the two references that the tilt of the microplates should face opposite to the axis of rotation.

Finally, not all the claim elements of the present invention are taught in the prior art. The rotors on the present invention are tilted away from the axis of centrifugation. All of the prior art references teach centrifuges with the rotors tilted toward the axis of rotation.

For these reasons the Examiner has failed to establish a *prima facie* conclusion of obviousness against Claim 29. In particular one of skill in the art would not have been motivated to combine the cited references. Neither reference alone or in combination, provides the necessary motivation to combine the references.. Thus, a *prima facie case* of obviousness has not been made and the rejection is improper. Accordingly, the rejection under 35 U.S.C. 103(a) should be withdrawn.

CONCLUSION

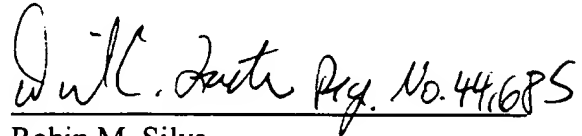
Applicants respectfully submit that the claims are now in condition for allowance and


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an early notification of such is solicited. If, upon review, the Examiner feels there are additional outstanding issues, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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MARKED-UP VERSION

In the Background of the Invention:

Please make all references to U.S. Patent Application Serial No. 08/815,975 read U.S. Patent 6,045,755 on page 2 lines 7, 10, and 11.

(Amended) The productivity of automated instruments can be dramatically improved by use of disposable reaction vessels (such as multititer plates or test tube arrays) into which reagents are added by pipetting, or by direct delivery from storage containers. The optimal storage vehicle is a syringe-like apparatus of a material inert to the chemical reactants, etc., e.g., a glass syringe, allowing the storage of the solution without any exposure to the atmosphere, and capable of serving as a delivery mechanism at the same time. See U.S. Patent [Application Serial No. 08/815,975] 6,045,755. An alternative technique based on the removal of upper layer of liquid by suction from the surface above the separated layers is limited to the arrays of up to a hundred of suctions (For similar situation in solid phase synthesis see U.S. Patent [Application Serial No. 08/815,975] 6,045,755. The present application is an improvement upon U.S. Patent nos 5,202,418, 5,338,831, 5,342,585, and [Application Serial No. 08/815,975] 6,045,755 which describe placement of resin in polypropylene mesh packets and removal of liquid through the openings of these packets, or removal of the liquid from the pieces of porous textile-like material by centrifugation, or removal of liquid phase from the solid phase by centrifugation of tilted plates. Liquid removal by centrifugation was described and is the subject of several publications (see the book "Aspects of the Merrified Peptide Syntheses" by Christian Birr in the series Reactivity and Structure Concepts in Organic Chemistry vol. 8, K. Hafner, J.-M. Lehn, C.W. Rees, P. von Rague, Schleyer, B.M. Trost, R. Zahradnik, Eds., Sringer-Verlag, Berlin, Heidelberg, New York, 1978, and German Patent Application P 20 17351.7, G. 70 13256.8, 1970. these references describe the use of centrifugation for liquid removal from slurry of solid phase particles in a concentric vessel equipped with a filtration material in its perimeter and spun around its axis. See also WO99/25470, hereby expressly incorporated by reference in its entirety.

In the Detailed Description of the Invention:

Please correct the following typographical errors:

(Amended) The stepwise solid phase synthesis of peptides is well known. An exemplary solid-phase combinatorial protocol is that for the synthesis of peptides attached to polymer resin, which proceeds according to Lam et al., 1991, Nature 354:82-84; U.S. Patent 5,510,240; Lam et al., 1994, Selective technology: Bead-binding screening. Methods: A Companion to Methods in Enzymology 6:372-380. Another exemplary protocol is that for the synthesis of benzodiazepine moieties, which proceeds according to Bunin et al., 1992, J. Amer. Chem. Soc., 114:10997-10998 and U.S. Patent 5,288,514. Also, for protocols for the addition of N-substituted glycines to form peptides, see, e.g., Simon, et al., 1992, Proc. Natl. Acad. Sci.

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USA, 89:9367-9371; Zuckermann et al., 1992, J. Amer. Chem. Soc., 114:10646-10647; WO PCT94/06,451 to Moos et al.; Approaches for synthesis of small molecular libraries were recently reviewed by, e.g., Krchnak and Lebl, 1996, Molecular Diversity, 1:193-216; Ellman, 1996, Account. Chem. Res., 29:132-143; Armstrong et al., 1996, Account. Chem. Res., 29:123-131.; Fruchtel et al., 1996, [Anaew] Angew. Chem. Int. Ed., 35:17-42; Thompson et al., 1996, Chem. Rev., 96:555-600; Rinnova et al., 1996, Collect. Czech. Chem. Commun., 61: 171-231; Hermkens et al., 1996, Tetrahedron, 52:4527-4554. Exemplary building blocks and reagents are amino acids, nucleosides, other organic acids, aldehydes, alcohols, and so forth, as well as bifunctional compounds, such as those given in Krchnak and Lebl, 1996, Molecular Diversity, 1:193-216.

The nucleic acids may contain any combination of deoxyribo- and ribo-nucleotides, and any combination of bases, both naturally occurring and synthetic, including uracil, adenine, thymine, cytosine, guanine, inosine, xanthine, hypoxanthine, isocytosine, isoguanine, etc. A preferred embodiment utilizes isocytosine and isoguanine in nucleic acids designed to be complementary to other probes, rather than target sequences, as this reduces non-specific hybridization, as is generally described in U.S. Patent No. 5,681,702. As used herein, the term "nucleoside" includes nucleotides as well as nucleoside and nucleotide analogs, and modified nucleosides such as amino modified nucleosides or phosphoramidite nucleosides. In addition, "nucleoside" includes non-naturally occurring analog structures. Thus for example the individual units of a peptide nucleic acid, each containing a base, are referred to herein as a nucleoside.

The stepwise synthesis of nucleic acids is well known, and generally involves the stepwise addition of protected, activated nucleoside monomers to a solid support, followed by deprotection steps and washing steps. See generally Gait, *Oligonucleotide Synthesis: A Practical Approach*, IRL Press, Oxford, UK 1984; [Eckstein,] incorporated by reference. This is generally done either with phosphoramidite or H-phosphonate nucleosides. This is generally done in one of two ways. First, the 5' position of the ribose is protected with 4',4'-dimethoxytrityl (DMT) followed by reaction with either 2-cyanoethoxy-bis-diisopropylaminophosphine in the presence of diisopropylammonium tetrazolide, or by reaction with chlorodiisopropylamino 2'-cyanoethoxyphosphine, to give the phosphoramidite as is known in the art; although other techniques may be used as will be appreciated by those in the art. See Gait, *supra*; Caruthers, *Science* 230:281 (1985), both of which are expressly incorporated herein by reference.

In the Claims

27. An apparatus comprising: a centrifuge comprising:
 a) a centrifuge comprising [a)] a rotor designed to hold reaction vessels at a tilt away from the axis of rotation; and

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b) a waste reservoir connected to said centrifuge to hold liquids expelled from said reaction vessels.

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PENDING CLAIMS

27. An apparatus comprising a centrifuge comprising:
 - a) a rotor designed to hold reaction vessels at a tilt away from the axis of rotation; and
 - b) a waste reservoir connected to said centrifuge to hold liquids expelled from said reaction vessels.
28. An apparatus according to claim 27 wherein said waste reservoir is connected to said centrifuge with a tube.
29. An apparatus according to claim 27 wherein said rotor comprises a plurality of holders, each holder designed to hold at least one microtiter plate.
30. An apparatus according to claim 27 further comprising a liquid distribution system.
31. An apparatus according to claim 30 wherein said liquid distribution system is integrated into the centrifuge.
32. An apparatus according to claim 27 further comprising a computer.